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EXAMINER	
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1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,489	WOOD ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36,39,40,42,43,51-60 and 64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36, 39-40, 42-43, 51-60, and 64-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/10; 4/14/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are pending. Applicants previously cancelled claims 1-27, 37-38, 41, 44-50, and 61-63. Receipt and consideration of Applicants' amended claim set, new IDS, and remarks/arguments submitted on February 3, 2010 and the new IDS submitted on April 14, 2010 are acknowledged.

Priority

The effective filing date of the instant application is February 24, 1995.

Election/Restrictions

The species elections for asthma as the respiratory disease in a mammal and corticosteroids as the elected therapeutic agent are maintained and remain in effect.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-36, 39-40, 51-60, and 64-72 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Radhakrishnan (U.S. Patent No. 5,049,389).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal comprising the steps of (a) providing an aerosol composition comprising aqueous droplets having a particle size of less than 10 microns in diameter, wherein the droplets comprise (i) water, (ii) crystalline particles of beclomethasone having an effective average particle size of less than 1,000 nm (i.e. at least 90% of the particles have a weight average particle size of less than about 1,000 nm, as

defined on pg. 16, lines 24-27 of Applicants' specification), (iii) at least one surface modifier adsorbed on the surface of the crystalline beclomethasone particles, and (b) administering the aerosol composition to the lungs of a mammal, wherein the respiratory disease is selected from the group consisting of ***asthma***, emphysema, respiratory distress syndrome, chronic bronchitis, and cystic fibrosis.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Liversidge teaches that dispersible particles consisting essentially **of crystalline poorly soluble drug substance having a surface modifier adsorbed on the surface thereof exhibit** unexpectedly higher bioavailability (title; abstract; col. 1, lines 5-10; col. 2, lines 34-37; and col. 3, lines 3-9). The **effective average particle size of the invented particles is less than about 400 nm** (abstract; col. 2, lines 38-43; col. 5, lines 25-40; claims 1-5). The phrase "**effective average particle size of less than about 400 nm" is defined to mean that at least 90% of the particles have a weight average particle size of less than about 400 nm** (col. 5, lines 25-28). **Preferably, at least 95% and more preferably, at least 99% of the particles have a particles size less than the effective average, such as 400 nm** (col. 5, lines 33-37). In some embodiments, the effective average particle size is less than about 100 nm (col. 5, lines 30-34). Suitable crystalline poorly soluble drugs include **anti-inflammatory agents and corticosteroids, and in preferred embodiments the drug substance is a steroid** (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). Suitable surface modifiers are disclosed from column 4, line 34 through col. 5, line 12 (e.g. sodium lauryl sulfate, lecithin, Pluronic F-68 [i.e. a polymer], etc.). The surface modifiers taught by Liversidge as being suitable are essentially ones

recited in Applicants' laundry list in claim 32, for example. **Suitable amounts of surface modifier are taught to be about 0.1-10 mg per square meter surface area of the drug substance (i.e. 0.1-90% w/w, preferably 20-60% w/w, based on the total weight of the dry particle)** (col. 7, lines 10-20).

Liversidge teaches **that the nanoparticles of crystalline drug substance may be obtained by conventional milling techniques, such as air jet and fragmentation milling** (col. 5, lines 50-61). Liversidge provides the necessary guidance to obtain nanocrystalline drug particles (see col. 5, line 41 through col. 7, line 29; claims 16-20). Liversidge teaches that the compositions may be delivered to mammals (e.g. claim 15).

Radhakrishnan teaches that **BECOTIDE® is an aqueous suspension of beclomethasone dipropionate that is conventionally administered by nebulization** (i.e. it is atomized from a nebulizer) to treat bronchial asthma (col. 5, lines 43-51). **BECOTIDE® is described by Radhakrishnan at col. 5, lines 43-51**. Beclomethasone dipropionate is art-recognized as being **a poorly water-soluble active agent** (col. 4, lines 22-23). Radhakrishnan measured the liquid droplet particle size of aerosolized BECOTIDE® expressed as mass median aerodynamic particle size (MMAD) in units of microns (Figure 4). Radhakrishnan also demonstrates that particles with a size of less than 1.1 microns reach the alveoli upon inhalation (Figure 3). According to Radhakrishnan's measurements, approximately 15% of the droplets have a particle size of about 400 nm or less and ~ 95% of the liquid droplets have a size of 10 microns or less (Figure 4 and col. 16, line 53 through col. 17, line 17).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

As far as can be ascertained at this time BECOTIDE® is silent as to the particle size and crystalline nature of the suspended beclomethasone dipropionate particles, as well as whether a surface active agent is adsorbed onto the surface of the crystalline beclomethasone particles and the quantity of surface modifier present. These deficiencies are cured by the teachings of Liversidge.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of Liversidge and Radhakrishnan, because modification of the teachings of Liversidge with those of Radhakrishnan concerning the commercial BECOTIDE® product would yield a inhalable pharmaceutical formulation comprising beclomethasone, which would reasonably exhibit a higher bioavailability. Furthermore, an ordinary skilled artisan would be motivated to utilize BDP, because Liversidge's invention is generally applicable to poorly water-soluble active agents, and BDP is an art-recognized poorly water-soluble active agent. Regarding the administration of BDP to treat asthma, BDP is a conventionally utilized to treat asthma, thus an ordinary skilled artisan would have been motivated to utilize BDP to treat a disease for which it is indicated.

Regarding the amount of surface modifier present in the composition administered, the combined prior art teaches overlapping amounts of surface modifier. The combined prior art teaches overlapping particle sizes and particle size distributions. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Furthermore, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art

would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Applicants' tabulated specification data is noted, and is not considered to demonstrate unexpected or surprising results. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 2/3/10 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by attacking the references individually and arguing that (1) the rejection is based on improper hindsight and ignores the guidelines set forth in MPEP § 2144.08 regarding obviousness and genus-species relationships; (2) allegedly Argument (1) is supported by the dicta in *Takeda Chemical Industries v. Alphapharm Pty.*, 492 F.3d 1350, 1357, 83 USPQ2d 1169, 1170 (Fed. Cir. 2007) describing the *Takeda* prior art as disclosing hundreds of millions of TZD compounds; and concluding that the *Takeda* prior art provided no motivation to select compound b from one of 54 specifically disclosed compounds, because there was no indication that compound b fell in the group of "the best performing compounds;" (3) the rejection allegedly fails to articulate a reasonable expectation of success; (4) the BECOTIDE® particle size disclosed in Radhakrishnan at column 16, lines 61-64 and at

column 16, line 66 through column 17, line 2 corresponds to the aqueous droplet particle size and is not comparable to the particle size of crystalline beclomethasone recited in Applicants' claims; and (5) Radhakrishnan allegedly teaches away from suspension formulations, because the beclomethasone in Radhakrishnan's formulations is solubilized inside the cholesterol-based liposomes invented by Radhakrishnan.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding (1), in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The motivation to select a poorly water-soluble crystalline drug being a steroid is not obtained from improper hindsight, but rather from the teachings of Liversidge (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). Furthermore, Radhakrishnan's description of the commercially available BECOTIDE® product as being an aqueous suspension of beclomethasone dipropionate provides ample evidence that

beclomethasone was conventionally prepared as a pharmaceutically acceptable aqueous suspension.

Applicants' reliance on *Takeda* is misplaced, because the facts of *Takeda* are not analogous to the facts of the instant application or the instant rejection. In *Takeda* the Federal Circuit considered whether it would have been obvious to select compound b from one of hundreds of millions of prior art-disclosed compounds indicated as exhibiting anti-diabetic properties, especially given that compound b had been described as exhibiting the undesirable properties of **causing "considerable increases in body weight and brown fat weight**." Applicants' citation from the *Takeda* decision cherry picks portions of the cited quotation to support their argument. The omitted part of the cited quotation from *Takeda*, when taken together with what Applicants cite, demonstrates that the fact pattern in *Takeda* is non-analogous to the instant application, because in *Takeda* the prior art taught away from the selection of compound b, whereas in the instant rejection the combined prior art does not teach away from the selection of beclomethasone. Thus, Applicants' reliance on *Takeda* to support argument (1) is unpersuasive. The rejection is maintained.

Argument (3) is unpersuasive, because it is not based on any objective evidence, but rather on Applicants' unsupported assertions. For example, Applicants do not explain why there would be no reasonable expectation of success upon following the teachings of Liversidge to modify the commercially available BECOTIDE® product described by Radhakrishnan (i.e. an aqueous suspension of beclomethasone particles). Applicants' arguments merely point to a statement in Liversidge (col. 7, lines 21-23) indicating that there is no guarantee that every combination of active agent and surface stabilizer will produce a stable nanoparticulate active

agent composition. Citation to Liversidge col. 7, lines 21-23 by Applicants suggests that only a guarantee of success meets Applicants' definition of a reasonable expectation of success. An absolute expectation of success is not the required standard for showing a reasonable expectation of success. Applicants' arguments also fail to note that in the sentence immediately following their Liversidge citation, Liversidge explicitly sets forth **a simple screening method** to ascertain whether a particular drug/surface stabilizer combination would yield a stable composition (Liversidge: col. 7, line 23-46). It is also noted that Liversidge's exemplifies stable aqueous formulations comprising danazol, which like beclomethasone, is a poorly water-soluble steroid active agent. Thus, argument (3) is unpersuasive. The rejection is maintained.

Regarding (4), Applicants cite Radhakrishnan at column 16, lines 61-64 and at column 16, line 66 through column 17, line 2 as teaching the liquid aerosol particle size (i.e. droplet particle size) of BECOTIDE®. Applicants are correct that the cited sections of Radhakrishnan describe droplet particle size, but this observation ignores (i) the fact that the instant rejection is based upon a combination of references; and (ii) the teachings of Liversidge, the primary reference of the instant rejection. Thus, argument (4) is an argument made by attacking the references individually without considering the teachings of the combined references.

Regarding (5), this argument ignores the first sentence of the section of the instant rejection describing the finding of obviousness as being based upon Radhakrishnan's description of the commercially available BECOTIDE® pharmaceutical product. The instant rejection is not based upon Radhakrishnan's teaching of liposomes, but rather on Radhakrishnan's description of the commercially available BECOTIDE®. Thus, Radhakrishnan is more of an evidentiary reference, because it is relied on to establish the characteristics of commercially available

BECOTIDE® at the time of Applicants' claimed invention. Furthermore, Radhakrishnan is not the primary reference of the instant rejection, but rather a secondary reference. Therefore, Applicants' citation of Radhakrishnan's teachings of liposome formulations misconstrues the basis of the instant rejection and is off point. Applicants' argument is unpersuasive. The rejection is maintained.

Claims 42-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Radhakrishnan (U.S. Patent No. 5,049,389) as applied to claims Liversidge et al. (U.S. Patent No. 5,145,684) in view of Radhakrishnan (U.S. Patent No. 5,049,389) above, and further in view of Spear et al. (U.S. Patent No. 5,525,623).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal as described above, wherein the nebulizing step is done using a jet nebulizer (claim 42) or an ultrasonic nebulizer (claim 43).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Liversidge and Radhakrishnan are set forth above.

Spear teaches that **jet nebulizers and ultrasonic nebulizers are conventional means of creating aerosols for use as asthma medication** (col. 13, lines 34-40).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Liversidge lacks the teaching of a jet nebulizer or an ultrasonic nebulizer. These deficiencies are cured by the teachings of Spear.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of the instant invention to nebulize an aqueous solution comprising beclomethasone dipropionate (BDP) using either an ultrasonic nebulizer or a jet nebulizer, because both nebulizers were conventionally used to administer pharmaceutical aqueous formulations. An ordinary skilled artisan would have been motivated and would have had a reasonable expectation of nebulizing an aqueous pharmaceutical formulation, such as that resulting from the teachings of Liversidge and Radhakrishnan, with a jet nebulizer or an ultrasonic nebulizer, because said nebulizers were conventionally known to be suitable for the inhalation administration of aqueous pharmaceutical formulations and were conventionally used for this purpose (Spear). The use of a device in the matter in which said device was intended to be used is prima facie obvious. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 2/3/10 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by reiterating the traversal arguments presented against the parent rejection based upon the teachings of Liversidge and Radhakrishnan

and indicating that Spear fails to cure the alleged deficiencies of Liversidge and Radhakrishnan. The Office's rebuttal arguments are herein incorporated by reference. The rejection is maintained and remains proper.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-33, 39-40, 51-60, 66, 69, and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claim 1 of copending '324 claims a sterile, stable, nanoparticulate dispersion comprising (i) a

liquid dispersion medium, (ii) nanoparticulate beclomethasone particles having an effective particle size of less than 150 nm, (iii) tyloxapol as a surface stabilizer adsorbed onto the surface of the beclomethasone nanoparticles, and (iv) optionally at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone.

The primary differences between the claim 28 of the instant application and claim 1 of copending '324 are that claim 1 of copending '324 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3) does not specify that the liquid dispersion medium is water, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1) and (3)-(4), these deficiencies are cured by the teachings of Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '324 evidences that it was contemplated for the beclomethasone nanoparticles to be crystalline. Thus, the formulation of the claimed nanoparticulate dispersions of copending '324 is an obvious modification of this formulation. Regarding particle size, the particle size recited in the claims of copending '324 overlap with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited

in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 9 of copending '324. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 39-40, 51-60, 66, 69, and 72 *prima facie* obvious over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed 2/3/10 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that according to MPEP §804 provisional obviousness-type double patenting rejections over later filed applications should be withdrawn to allow the earlier filed application to issue without filing a terminal disclaimer. Applicants' argument is unpersuasive, because according to the quoted section of MPEP § 804 it is only proper to withdraw provisional obviousness-type double patenting rejection, when the provisional obviousness-type double patenting rejection is the only remaining rejection. The instant provisional obviousness-type double patenting rejection is **not** the only remaining rejection. Therefore, it is improper to withdraw this rejection. The rejection is maintained.

Claims 28-33, 53-60, 66, 69, and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No.

5,049,389). Independent claim 28 of the instant application is described above. Independent claim 60 of copending '194 claims a method of treating a subject in need of either symptomatic or prophylactic treatment comprising administering to said subject an effect amount of sterile particulate fluticasone composition comprising (i) particles of fluticasone (i.e. an anti-inflammatory steroid) having an effective average particle size of less than 150 nm and (ii) at least one surface stabilizer.

The primary differences between claim 60 of copending '194 and claim 1 of the instant application are that claim 60 of copending '194 does not (1) specify that the disease being treated is a respiratory disease (e.g. asthma); (2) does not recite particles of beclomethasone; (3) does not specify that the particulate composition is an aqueous dispersion; and (4) does not specify that the particulate active agent is crystalline. Deficiencies (2)-(3) are cured in part by the teachings of Liversidge and Radhakrishnan set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Liversidge also establishes that anti-inflammatory steroids are suitable for incorporation into nanoparticulate dispersions (col. 3, lines 53-55 and 64; col. 4, lines 25-26; Example 1 through Example 14: col. 8, line 35 through col. 13, line 53). Regarding deficiencies (1) and (4), dependent claims 64-65 and 69 evidence that it is obvious to modify the claimed method of treatment of copending '194 to treat asthma and to utilize crystalline particulate fluticasone in the administered composition, respectively. Regarding particle size, the particle size recited in the claims of copending '194 overlap with the particle size ranges recited in the instantly rejected

claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 76 of copending '194. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 53-60, 66, 69, and 72 *prima facie* obvious over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed 2/3/10 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by arguing that according to MPEP §804 provisional obviousness-type double patenting rejections over later filed applications should be withdrawn to allow the earlier filed application to issue without filing a terminal disclaimer. Applicants' argument is unpersuasive, because according to the quoted section of MPEP § 804 it is only proper to withdraw provisional obviousness-type double patenting rejection, when the provisional obviousness-type double patenting rejection is the only remaining rejection. The instant provisional obviousness-type double patenting rejection is **not** the only remaining rejection. Therefore, it is improper to withdraw this rejection. The rejection is maintained.

Claims 28-36 and 51-60 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claims a nanoparticulate composition comprising (i) beclomethasone dipropionate particles having an average particle size of less than about 1,000 nm and (ii) at least one surface modifier.

The primary differences between the claim 28 of the instant application and claim 1 of copending '092 are that claim 1 of copending '092 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3) does not recite an aqueous dispersion medium, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1)-(2) and (4), these deficiencies are cured by the teachings of Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is desirable to use nanoparticulate crystalline solids in a liquid dispersion medium to obtain formulations exhibiting unexpectedly improved bio-availability; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '092 evidences that it was contemplated for the beclomethasone nanoparticles to be formulated as an aqueous dispersion. Thus, the formulation of the claimed nanoparticulate beclomethasone dipropionate of copending '092 is an obvious modification of this formulation. Regarding particle size, the particle size range recited in the claims of copending '092 overlaps with the particle size ranges recited in the

instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 17 of copending '092. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-36 and 51-60 *prima facie* obvious over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

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Conclusion

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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